

# **HYBRID SIMULTANEOUS INTEGRATED BOOST TECHNIQUE IN LOCALLY ADVANCED TONGUE CANCER-A PROSPECTIVE STDUY**



A dissertation submitted to  
the Tamil nadu Dr. M.G.R. Medical University, Chennai,  
in partial fulfilment of the requirements for the award of the degree of  
**DOCTOR OF MEDICINE (M.D.) IN RADIOTHERAPY**

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## CERTIFICATE

This is to certify that this dissertation titled, “**HYBRID  
SIMULTANEOUS INTEGRATED BOOST  
TECHNIQUE IN LOCALLY ADVANCED TONGUE  
CANCER-A PROSPECTIVE STDUY**” is a bonafide record of the work done by Dr. Vijayaveeran.P, in the Division of Radiation Oncology, Cancer Institute (W. I. A.), Chennai, during the period of his postgraduate study for the degree of M.D. (Branch X – Radiotherapy) from 2014-2017 under my direct guidance and supervision.

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**INTRODUCTION:**

Head and neck cancer is the sixth most common cancer worldwide.(1) 50% of the overall global head and neck cancer burden is from Asia, India in specific. (2)Each year 2 lakhs new patients are diagnosed and 1 lakh patient die with oral cavity cancers.(3) In India carcinoma buccal mucosa and carcinoma tongue are more common among the oral cavity cancers. Carcinoma tongue is second most common cancer of oral cavity. It is more common in men compared to women. The ratio is 3:1 in sex distribution.(4) The incidence of carcinoma tongue according to Madras Metropolitan Tumour Registry (MMTR)

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## **I.INTRODUCTION:**

Head and neck cancer is the sixth most common cancer worldwide.(1) 50% of the overall global head and neck cancer burden is from Asia, India in specific. (2)Each year 2 lakhs new patients are diagnosed and 1 lakh patient die with oral cavity cancers.(3) In India carcinoma buccal mucosa and carcinoma tongue are more common among the oral cavity cancers. Carcinoma tongue is second most common cancer of oral cavity. It is more common in men compared to women. The ratio is 3:1 in sex distribution.(4) The incidence of carcinoma tongue according to Madras Metropolitan Tumour Registry (MMTR) is 10.3 /100000 population for the year 2012-13. (5)

Incidence rates for the year 2012-13.

Source	Sex	CIR	ASR	No of cases	Total cases
World GLOBOCAN (Oral cavity)	Male	5.6	5.5	198975	7410376
	Female	2.9	2.5	101398	6657518
India IARC (Oral cavity)	Male	8.3	10.1	53842	477482
	Female	3.8	4.3	23161	537452
Chennai MMTR (Tongue)	Male	8.1	7.4	380	5448
	Female	2.2	2.0	101	6219

## 1).INSTITUTE DATA

609 patients presenting to the Institute from 2006 to 2011 are diagnosed with carcinoma tongue. Most of the patients report to the institute in locally advanced stages. Stage wise 5 years Disease free survival (DFS) and 5 year Overall survival (OS) is given below.

Stage	Total cases	DFS	5 years OS
I	87	52%	74%
II	122	36%	50%
III	160	40%	46%
IV	237	19%	23%

5years Relative survival of Oral cancer (1988-2001) from SEER database (6).

	Tongue (%)	Oral Tongue (%)
Stage I	70.7	75.9
Stage II	58.6	57.5
Stage III	47.3	38.8
Stage IV	36.7	26.5

Distribution of treatment modalities used in our institute from 2006 -11

Treatment modality	No of cases	Percentage
Concurrent chemo-radiation	327	54%
Radiation alone	170	28%
Surgery followed adjuvant Radiation	58	9.5%
Surgery followed by concurrent chemo-radiation	36	6%
Surgery alone	16	2.5%
Surgery followed by chemotherapy	1	<0.2%
Palliative chemotherapy	1	<0.2%
Total	609	

5 Years DFS and 5 years OS with concurrent chemo-radiation and Radiation alone are given below.

Treatment	DFS	5 years OS
RT+CT	30%	38%
RT alone	36%	19%



## **2).RISK FACTORS FOR TONGUE CANCER:**

The common causes for tongue cancer are

Five S's

Smoking

Spirit (alcohol)

Sharp (Septic) tooth

Spicy food

Syphilis

### **SMOKING AND ALCOHOL:**

Use of tobacco and alcohol is associated with 80-90% of all case of carcinoma tongue. A Case control study with two arms, smoking alone and smoking along with alcohol showed that smoking increases the risk of developing cancer by about 25 times than in non-smokers.(7) Tobacco in any form increases the risk of development tongue cancer by three folds. Both smoking and alcohol have synergistic effect and will increase incidence of cancers. Stopping smoking for more than 9 years will decrease the incidence of oral cancer by about 50 %(8). Second primary is more common in patients who smoke. Continuation of smoking during treatment results in a poor outcome.

**Carcinogen in Tobacco:**

Aromatic hydrocarbons benzopyrene,

Tobacco specific nitrosamines (TSNs),

N-nitrosononicotine (NNN),

N-nitrosopyrrolidine (NPYR),

N-nitrosodimethylamine (NDMA),

4-methylnitrosamino-1-(3-pyridyl)-1-butanone (NNK).

**Mechanisms of tobacco carcinogenesis:**

These products will act on ketatinocyte stem cells. They produce DNA adducts (O-6-methylguanine) which interfere and disrupt the accuracy of DNA replication producing mutations, Leading to chromosomal instability. (9)

**Mechanisms of alcohol synergism:**

- 1) Alcohol increases the permeability of carcinogens in oral mucosa
- 2) It will produce poor oral hygiene.
- 3) It will reduce detoxification in liver for active carcinogens

## **NON SMOKING CAUSE OF ORAL CANCERS:**

DIETARY

OCCUPATIONAL

ENVIRONMENTAL

LICHEN PLANUS:

It will progress to malignant transformation in around about 0.3% patients. It is also associated with tobacco usage.

GRAFT VERUS HOST DISEASE

VIRUS:

1) Human papilloma virus (HPV):

Up to 20% of oral cavity cancer shows HPV 16 DNA.

2) HIV infection

3) Herpes simplex virus(HSV)

4) Epstein-barr virus(EBV)

5) Hepatitis C virus.(HCV)

Fungal infection:

Candida albicans produce leucoplakia than may show malignant transformation.

## CANCER SYNDROMES associated with carcinoma tongue

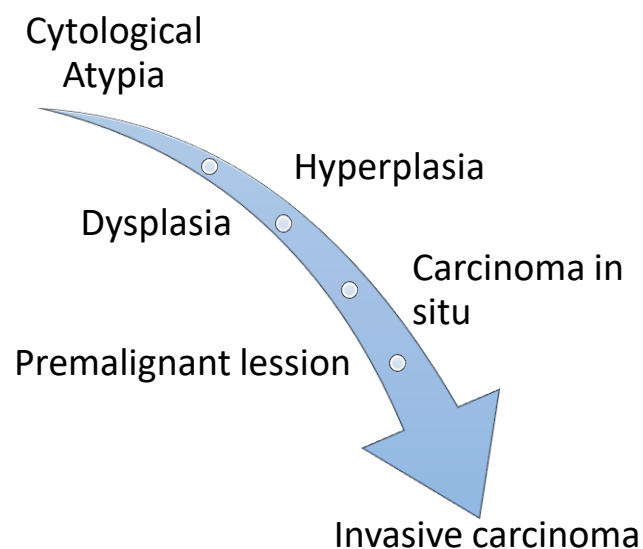
Xeroderma pigmentosum

Ataxia telangiectasia

Li fraumeni syndrome

Fanconi's anemia

### **NATURAL HISTORY:**



Patients most commonly present with chronic non healing ulcer with or without pain, young women may present with white patch-leukoplakia. Also difficulty in speech and swallowing. Tongue cancers grow rapidly either infiltrative or exophytic. Infiltrative tumours may be very large at presentation. Thick tumours have worse prognosis. Thickness >4 mm increased probability of occult metastasis to neck nodes.(10)

### **3).HISTOPATHOLOGY:**

#### **Squamous cell carcinoma:**

It is most common. Seen in 90% cases. It has several variants, mostly Basaloid and verrucous carcinoma.(11)

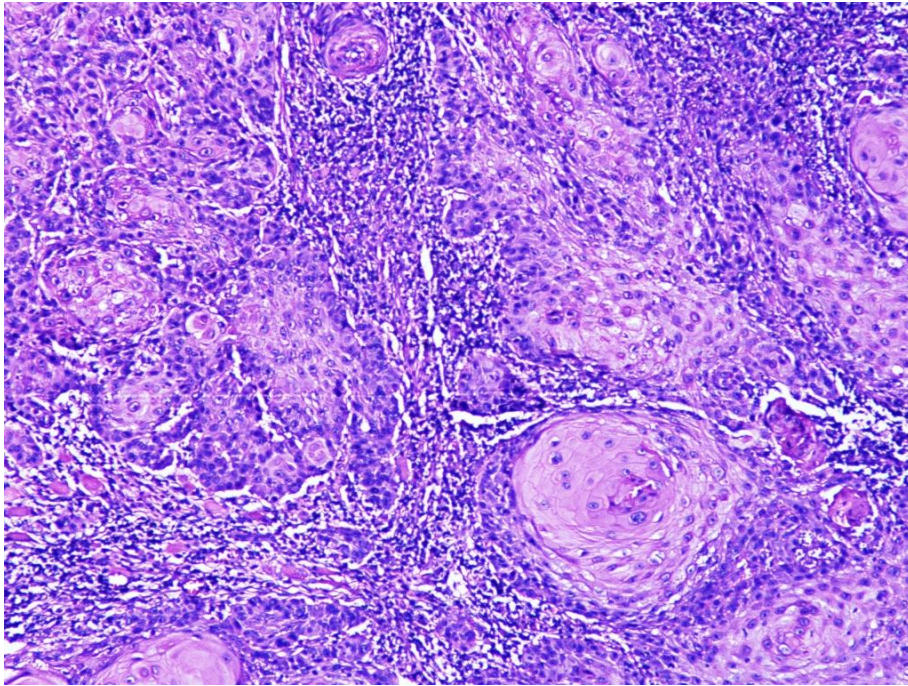
#### **Basaloid squamous cell carcinoma:**

It has worse prognosis than normal squamous cell carcinoma. It is associated with advance disease, distant metastasis and poor overall survival.

#### **Verrucous squamous cell carcinoma:**

It is less common variant. It is a low grade malignancy with good local control and good overall survival. It presents as a thickened white patchy mucosa in early stages. But in advanced stage it looks like velvety exophytic lesion.

Treatment is excision of the lesion but it is prone to recur after excision.



**Non squamous cell carcinoma:**

Adenocarcinoma,

Melanoma,

Lymphoma,

Leiomyosarcoma,

Kaposi's sarcoma.-mostly in oral cavity (gingiva, palate and tongue). After

HAART treatment incidence decreased into 50%

Adenosquamous carcinoma,

Papillary squamous cell carcinoma,

Sarcomatoid carcinoma

**Prognostic factors in histology:**

- 1) Tumour margins
- 2) Perineural invasion
- 3) Histopathology of tumour
- 4) Grade of tumour
- 5) Lymphatic/vascular invasion
- 6) Angiogenesis.

**4).PREMALIGNANT LESSIONS:****Leukoplakia:**

It has two types homogenous and nonhomogenous.

Homogenous: uniform white lesion and low (<1%) malignant potential.

Non homogenous: nodular, sparkled lesion with central ulceration. It has more malignant potential. It has 18 % progress to cancer.(12)

Leukoplakia will regress spontaneously no treatment needed. Need to do biopsy for malignant transformation. If it shows dysplastic changes we have to do excision of the lesion. Leukoplakia will occur 6 folds more in smokers compared to non-smokers

**Oral hairy leukoplakia:**

It is due to virus infection of oral cavity. Malignant transformation is less common.

### **Erythroplakia:**

It is chronic red patch on the mucosa. If erythroplakia is present we have find out other erythematous lesion in the patient. It has very high potential for malignant transformation compare to other pre malignant lesions. Erythroplakia progress to invasive carcinoma about 51%, carcinoma in situ about 40% and mild to moderate dysplasia about 9%. We have to do surgical excision of all erythroplakia lesions.

### **5).ANATOMY OF TONGUE:**

Parts of oral cavity:

It has lips, oral tongue, floor of mouth, alveolar ridge, retromolar trigone, hard palate and buccal mucosa.

Tongue:

It is a muscular structure in oral cavity, triangle in shape, root of tongue attached to mandible and hyoid bone. It is divided in to two parts by a V shaped terminal sulcus marked by circumvallate papillae, anterior two third (oral tongue) - part of oral cavity, posterior one third (base of tongue) –part of oropharynx.

Functions: Taste, chewing, swallowing and speech.



Anterior two third of tongue:

It has five parts tip, dorsal surface, ventral surface, right and left lateral borders.

Dorsal surface of tongue:

Papillae: Superior surface of tongue covered by mucosal folds having taste buds called as papillae for taste.

- 1) Filiform papillae: cone shaped distributed throughout dorsum of tongue
- 2) Fungiform papillae: round shaped predominantly in the border.
- 3) Circumvallate papillae: cylindrical shaped in 8-12 in number arranged in signal V shaped line anterior to terminal sulcus.
- 4) Foliate papillae: Linear shaped border of tongue near terminal sulcus.

Ventral surface of tongue:

Frenulum: tongue is divided in to right and left half by sagittal septum.

Frenulum is median fold of mucosa overlying lower margin of sagittal septum.

On each side of frenulum lingual veins present.

Pharyngeal surface: base of tongue - sub mucosal lymphoid tissue which forms the lingual tonsil.

Muscles:

Intrinsic muscle originate and inserted within the substance of tongue.

They are responsible for the shape of tongue. Extrinsic muscle originate from

structures outside tongue and inserted in to the tongue. They are responsible for movement of tongue and tumour infiltrated causes ankyloglossia.

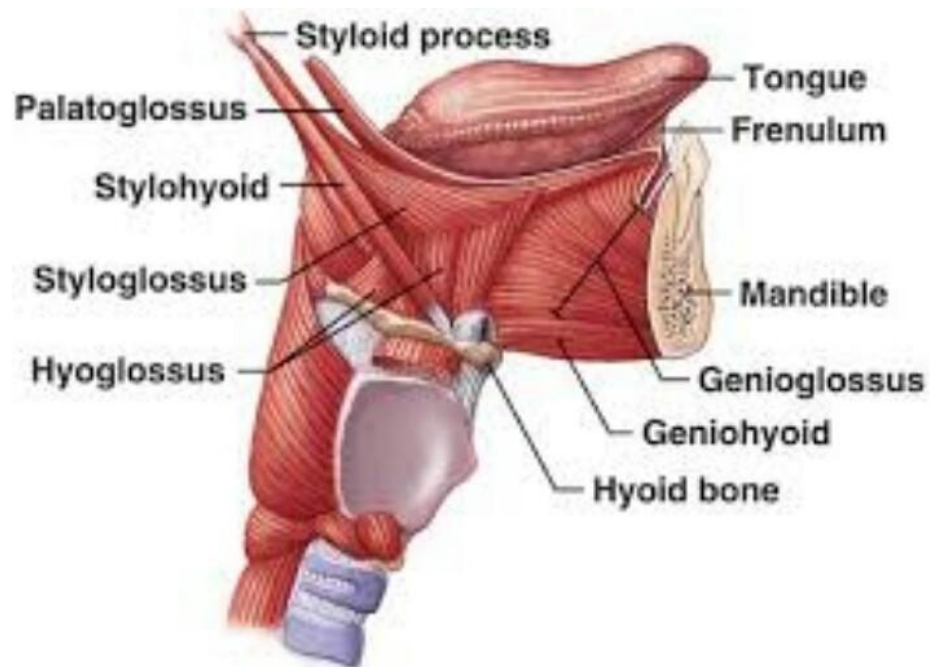


Figure shows Extrinsic muscles of the tongue

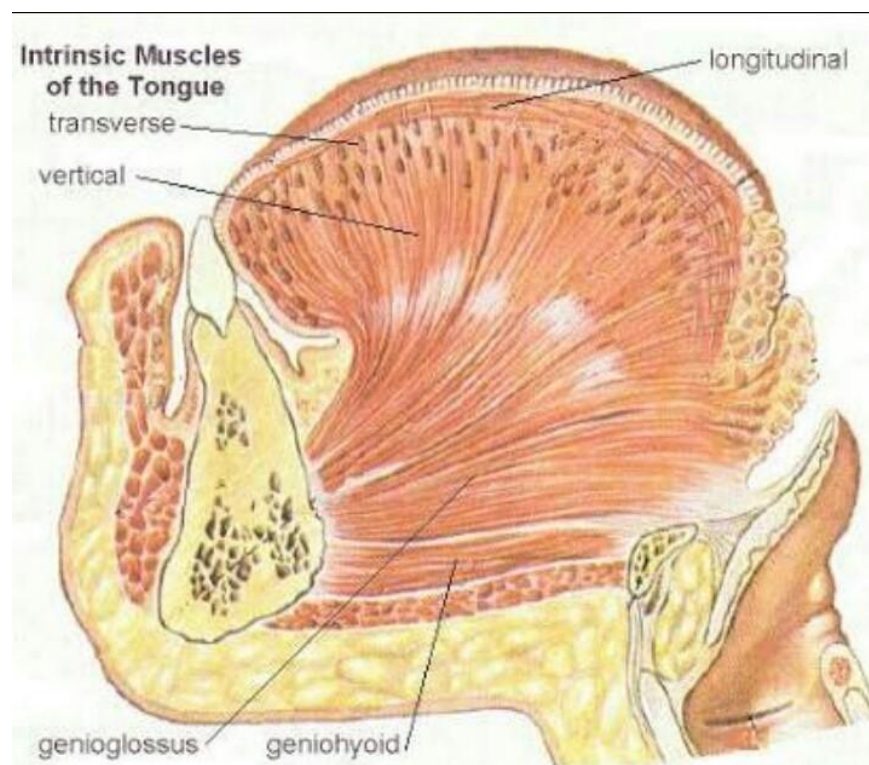


Figure shows Intrinsic muscles of the tongue

Muscles of tongue:

<b>Muscles</b>	<b>Origin</b>	<b>insertion</b>	<b>innervation</b>	<b>Functions</b>
<b>Intrinsic muscles</b>				
Superior longitudinal	Base of tongue and median septum		Hypoglossal nerve (XII)	Shorten tongue, curl tip and sides
Inferior longitudinal	Root of tongue	Apex of tongue	Hypoglossal nerve (XII)	Shorten tongue, uncurls tip and turns down
Transverse	Median septum	Lateral border	Hypoglossal nerve (XII)	Narrow and elongates
Vertical	Dorsum of tongue	Ventral region	Hypoglossal nerve (XII)	Flatten and widens

Muscles	Origin	insertion	innervation	Functions
Extrinsic muscle				
Genioglossus	Mandible(Mental tubercle)	Entire tongue and hyoid bone	Hypoglossal nerve (XII)	Protrusion
Hyoglossus	Hyoid bone( greater horn)	Lateral surface	Hypoglossal nerve (XII)	Depression
Styloglossus	Styloid process	Lateral surface	Hypoglossal nerve (XII)	Retraction
Palatoglossus	Palatine aponeurosis	Lateral border	Vagus nerve(X)	Swallowing

Arterial supply:

Lingual artery: it is a major artery of tongue, originate from external carotid artery. Tonsillar and ascending pharyngeal arteries also supplies oral tongue.

Venous drainage:

Deep lingual vein: it is visible in ventral surface of tongue. It ends in to internal jugular vein. Dorsal lingual vein also drains from tongue and ends in to internal jugular vein.

Nerve supply:

Motor supply: All intrinsic and extrinsic muscles are innervated by hypoglossal nerve except palatoglossus is innervated by vagus nerve.

Lymphatic drainage:

It has five primary level.

Level I: IA- sub mental and IB- submandibular node.

Level II: Upper jugular group of lymph nodes.

Level III: Mid jugular group of lymph nodes.

Level IV: Inferior jugular group of lymph nodes (Supraclavicular lymph node).

Level V: Posterior triangle group of lymph nodes.

Lymphatic drainage of tongue:

Anterior tongue drains in to sub mental (level IA).

Lateral border of tongue drains in to submandibular nodes (level IB) and upper

jugular group of lymph nodes (level II).

Posterior tongue drains in to upper jugular group of lymph nodes (level II).

Tongue is midline structure it cause bilateral lymph node metastasis.

Skip metastasis: some patient will get level IV lymph node metastasis without involving level I, II and III.

Salivary glands: parotid gland, sub mandibular gland and sub lingual gland.

Mandible: It has ramus and body ramus has medial surface, lateral surface, condylar process and coronoid process. Lateral surface of ramus provide attachment to massicator muscle.

Posterior and inferior border intersect to form angle of mandible.

Coronoid process flat triangle process at the junction of superior and anterior border provides attachment for temporalis muscle. Condylar process at the junction of posterior and superior border, has two parts head and neck. Head form tempromandibular joint, neck provides attachment for lateral pterygoid muscle.

Medial surface from lateral wall of infratemporal fossa provides attachment to medial pterygoid muscle, it has mandibular foram, inferior alveolar nerve passed through it.

Temporo-mandibular joint:

It mandible articulate with temporal bone. When tumour infiltrates TM joint patients cannot open mouth. It will cause trismus. Its difficult assess the oral cavity with trismus.

**STAGING:**

<b>T stage</b>	<b>Description</b>
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour 2 cm or less in greatest dimension
T2	Tumour more than 2 cm but less than 4 cm in greatest dimension
T3	Tumour more than 4 cm in greatest dimension
T4a	Tumour invades adjacent structures. Eg. cortical bone, deep(extrinsic)muscles of tongue ( genioglossus, hyoglossus, palatoglossus and styloglossus), maxillary sinus and skin of face.
T4b	Tumour invades masticator space, pterygoid plate, or skull base or encases carotid artery.

<b>N stage</b>	<b>Description</b>
Nx	Regional lymph node cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2a	Metastasis to a single ipsilateral lymph node, > 3 cm but < 6 cm in greatest dimension
N2b	Metastasis to multiple ipsilateral lymph node, not more than 6 cm in greatest dimension
N2c	Metastasis to bilateral or contralateral lymph node, not more than 6 cm in greatest dimension
N3	Metastasis to a lymph node more than 6 cm in greatest dimension

<b>M stage</b>	<b>Description</b>
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present



Stage group	TNM stage
0	Tis N0 M0
I	T1 N0 M0
II	T2 N0 M0
III	T3 N0 M0, T1 N1 M0, T2 N1 M0 or T3 N1 M0
Iva	T4a N0 M0, T4a N1 M0, T4a N2 M0, T1 N2 M0, T2 N2 M0, T3 N2 M0 or T4a N2 M0
IVb	Any T N3 M0, T4b any N M0
IVc	Any T any N M1



Figure shows T4a tongue lesion with ankyloglossia

## **ORAL CAVITY EXAMINATION:**

Simple visual inspection:

We have to see tongue surface for description of the lesion (ulcerative, proliferative, exophytic, endophytic, fungating tumour) and mobility for muscle infiltration or hypoglossal nerve damage.

Palpation:

We can demonstrate the three dimension view of tumour, consistency and tongue fixation. Tumour in tongue starts as small painless ulcer than progress to invade the muscle of tongue. Squamous cell carcinoma of tongue commonly present in lateral border of tongue. Bimanual examination of oral cavity will assess the depth of invasion of tongue tumour.

Examination of head and neck cancer: it includes inspection and palpation of skin over face, scalp, oral cavity, nasal cavity, nasopharynx, ear, oropharynx, hypo pharynx and larynx. Than examination of cervical lymph nodes and cranial nerves. Tumour around 30% to 40% will has cervical lymph node metastasis. Patients die due to uncontrolled local disease with haemorrhage and aspiration. Distant metastasis is rarely seen before death. 19% patients may developed second malignancy in upper aero-digestive track which is attributed to “Field cancerization”.(13)

## **6).INVESTIGATION:**

### Basic

- 1) Routine blood investigation,
- 2) Viral markers,
- 3) ECG

### Diagnostic

- 1) Biopsy from tumour

### Staging

- 1) Endoscopy (Direct laryngoscopy and pharyngoscopy)
- 2) X ray chest PA view
- 3) CT scan head and neck.
- 4) MR image head and neck.
- 5) PET CT scan

## **7).TREATMENT:**

### **Curative intent of treatment**

Surgery is main modality of treatment for early stage carcinoma tongue. Early stage disease treated with surgically with adequate margins followed by adjuvant treatment depends upon histopathologically.

Late stage disease is approached with multimodality treatments

(Surgery, radiation and chemotherapy).

Ultimate aim of treatment:

- 1) Cure the cancer,
- 2) Restore the function
- 3) Minimize the complication of treatment
- 4) Prevent metastasis.

Selection of single or combined treatment modality depends on stage, size and site of the tumour. Multidisciplinary team assessment should be done before starting treatment of tongue cancer. It includes surgical oncologist, medical oncologist, radiation oncologist, nursing staff, dentist, speech therapist, dietician and counsellor for family & social support.

NCCN (National Comprehensive Cancer Network) recommend early stage lesion will treated with single modality of treatment (surgery or radiation). Advance stage lesion treated with combined modality treatment.

Factors affecting treatment modality:

- 1) Location of the tumour,
- 2) Size of the tumour,
- 3) Cervical lymphadenopathy,
- 4) Histology
- 5) Previous treatment
- 6) Age and comorbidity
- 7) Socio-economic status.

**Early stage disease (Stage I, Stage II):**

Surgery alone: T1- Local excision with margin, T2- Partial glossectomy

Brachytherapy alone: Hairpin technique, Plastic tube loop technique

Surgery preferred over brachytherapy in

- 1) Bone involvement
- 2) Melanoma
- 3) Adenocarcinoma
- 4) Tip of the tongue lesion
- 5) Tumour surrounding by pre malignant lesion
- 6) Syphilitic glossitis.

## **ADVANCED STAGE DISEASE:**

### **Surgery:**

Subtotal or total glossectomy

Marginal/segmental mandibulectomy

With free tissue transfer or regional pedicled flaps

Approach:

Median or para-median mandibulotomy, Trans-cervical

### **Management of Neck:**

Primary lesion <2 mm-neck is managed expectantly

Larger lesion (including N0)-Selective neck dissection of levels I to IV

Lesions close to, or involving the mid line- Bilateral neck dissection

Postoperative RT indications: it is decrease local recurrence

1. Close or positive margins,
2. Extra-capsular invasion,
3. Bone invasion,
4. Pathological node positive disease,
5. Lymphovascular and perineural invasion.

## **RADIATION:**

External Beam Radiotherapy upto 40 Gy followed interstitial brachytherapy. Decroix and Ghissein study showed combine external beam radiation and brachytherapy to be beneficial (14)

Concurrent chemo-radiotherapy:

Concurrent chemo-radiation will increase the overall survival in locally advanced head and neck cancer is about 5% and absolute benefit in survival 8% in five years.(15)

Salvage surgery:

It is the second attempt at cure after definite treatment or final attempt for cure in recurrent disease following surgery, radiation and chemo-radiation. It is only cure option available and mainly final curative attempt.

Palliative intent of treatment:

Patients with more advanced disease not curable disease will be treated with palliative to reduce the symptoms (like pain, bleeding and reduce the burden of the disease). It may be surgery, radiation and chemotherapy.

Radiation used to relieve the pain, bleeding as in palliative treatment.

Chemotherapy used in metastatic disease. Surgery is mainly used to debulk the tumour size and reduce the burden of disease

## **SURGERY:**

Selecting the type, approach and extend of surgery depends on size, site and depth of the infiltration and proximity of tumour from mandible or maxilla, supine Position: 30 degree angle and anaesthesia.

Anaesthesia:

Small lesion are excised with local anaesthesia.

Larger lesion require General anaesthesia with Naso-tracheal tube intubation.

Surgical approach:

1. Trans-oral,
2. Lower cheek flap
3. Mandubulotomy
4. Trans cervical

With

- 1) Healing by secondary intension,
- 2) Primary closure,
- 3) Split thickness skin grafts
- 4) Free tissue transfer or regional pedicled flaps



## **RADIATION THERAPY:**

Radiation treatment can be given as teletherapy, brachytherapy and internal therapy.

Mechanism of action of Radiation:

Radiation will have two types of action, Direct action and indirect action. Direct action is fast moving electron interact direct with DNA molecule and cause DNA damage. Indirect action is fast moving electron will interact with other atoms or molecules in the cell. This will produce free radicals and free radical will cause DNA damage. Radiation will produce cell DNA damage by double-strand or single-strand breaks. Double strand breaks will leads to cell death. Single strand breaks will cause sub lethal DNA damage, it may repair by themselves. Before repair that cell will undergone one more single-strand break than this may leads to cell death. But the repair mechanism is superior in normal cell compared to cancer cells. Cell death means cells unable to divide furthermore and cause growth and spread of disease. Chromosomal aberration will leads to cell death while they attempt to divide after lethal dose of radiation (mitotic cell death).

Aim of the radiation is to deliver precise measured dose to the target volume and minimal damage to the normal surrounding tissue.

## **BRACHYTHERAPY:**

It is form of radiotherapy where the source of the radiation is kept very close to the tumour or actually implanted in to the tumour. Iridium-192 is commonly using radioactive source in most of the cancers. It has low photon energy makes protection easier than the Radium or Cesium-137. It gives high dose to tumour by a short period of time and we can spare adjacent normal tissue. Brachytherapy gives the benefit of function preservation, which is achieved through tissue preservation. Local control rates are 85% which are on par with that achieved by surgery. Local control rates decrease with increasing tumour size. (16)

Brachytherapy techniques in tongue:

### 1) Hairpin technique:

Implant is in the shape of hairpin, the two limbs are 12 mm apart and 6 cm in length. This forms a double plan. Single plan implantation is not preferred as it does not cover deeper parts. Stainless steel slotted hairpin guides are inserted under general anaesthesia. First anterior most and posterior most hairpin guides are implanted and later the required number of guides are incorporated between them, with a 12 mm gap between them. The limbs are cut depending upon the tumour depth. Top of the tumour is adequately covered by the bridge of the hairpin. In order to

cover bottom adequately limb of the hairpin should be longer than the tumour.

## 2) Plastic tube loop technique:

It is used for larger volume tumour difficult to cover with hairpin implants. Plastic tubes is formed in to a loop, this also a two plan implant. Stainless steel guide needles are pushed into the tumour from the skin below in jaw line.

## Brachytherapy Vs External Beam Radiation Therapy (EBRT)

Local control rates are suboptimal in EBRT in contrast to brachytherapy

## LDR Vs HDR brachytherapy:

HDR brachytherapy schedule- 59 Gy in 6 Gy twice daily compared to

LDR brachytherapy schedule- 61 Gy over 5 to 6 days showed inferior local

control rates with HDR (T1: 85% Vs 64%, T2: 71% Vs 38%) (17)

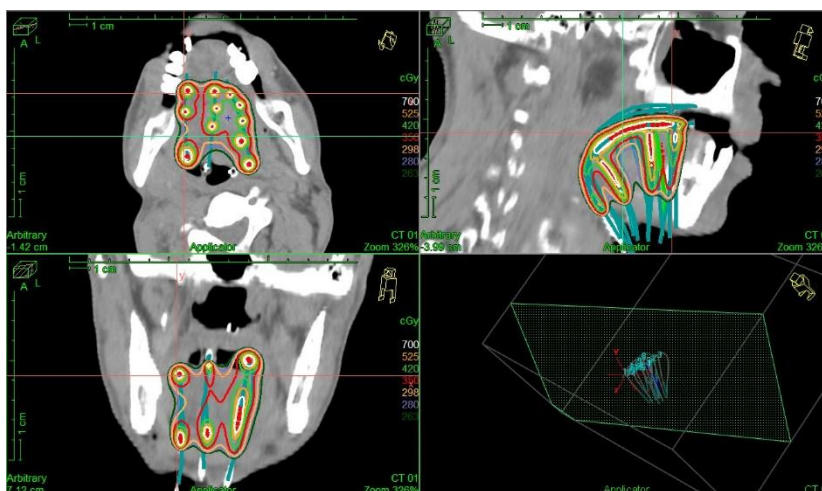


Figure shows Brachytherapy planning for carcinoma tongue.

## **EXTERNAL BEAM RADIATION THERAPY**

It is a modality of radiation delivery in which the source of radiation is at a distance from the human body. The radiation source may be a radioactive nuclide, Cobalt 60 emitting Gamma rays, is used presently, or it may be X-rays Produced by a Linear Accelerator, Electrons, protons, heavy charged particles etc. Accuracy of treatment delivery is of utmost importance.

Positioning the patient:

Patient in supine position, straight and neck extended. We have to place custom-made mouth bite to depress the tongue. Because we have to avoid radiation dose to hard palate and parotid glands. Than patient should be immobilized with thermoplastic mould or perspex. It is helped to fix the well-defined position to treat the patient.

If a patient is having short neck, both shoulders should be depressed by tensioning device to loop the feet. Because we have to treat whole neck region. Effective immobilization will reduce setup error.

Radiation techniques:

- 1) 2D conventional technique
- 2) 3D conformal technique
- 3) IMRT technique
- 4) Rapid arc technique.

## **2D CONVENTIONAL TECHNIQUE:**

Target volume includes primary tumour with 2 cm margin and ipsi lateral submandibular and upper deep cervical nodes.

Early lesion in lateral tongue is treated using anterior and lateral wedged fields, this gives homogenous dose distribution with sparing of contralateral oral cavity and spinal cord. For large tumours near or crossing midline two opposing lateral fields are used. Anterior and lateral wedged fields produce less mucositis and xerostomia compared to two opposing lateral fields used in extensive tumour.

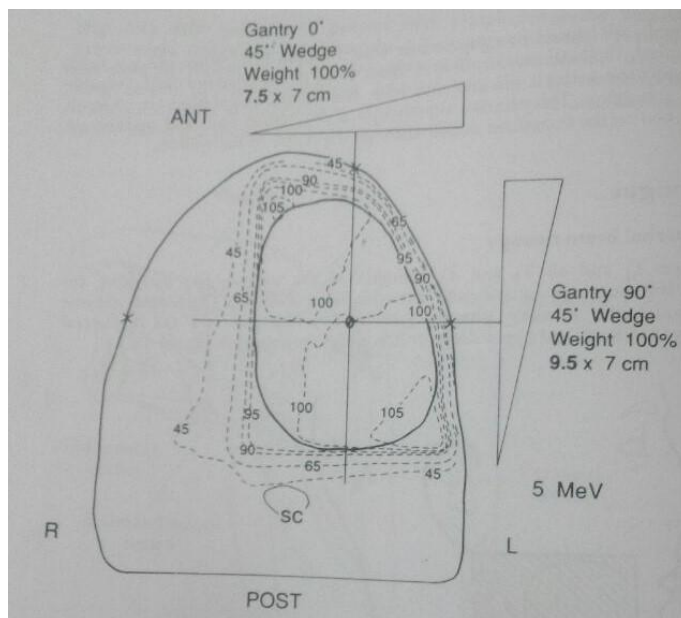


Figure shows 2D wedge field technique for carcinoma tongue

RT field borders in two opposing lateral fields:

Superior border: 2 cm above the primary lesion,

Inferior border: below hyoid bone,

Anterior border: 2 cm front of primary tumour (usually in front of mandible),

Posterior border: back to the vertebral corpuses.

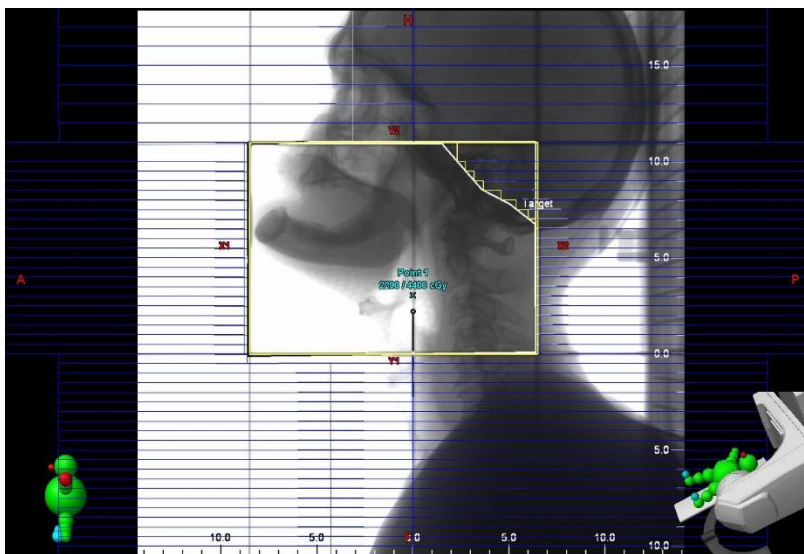


Figure shows 2D planning with MLC shielding of lateral field

Supraclavicular field border:

Superior border: inferior border of lateral fields,

Inferior border: bottom supraclavicular joint,

Lateral border: including medial two third of clavicle.

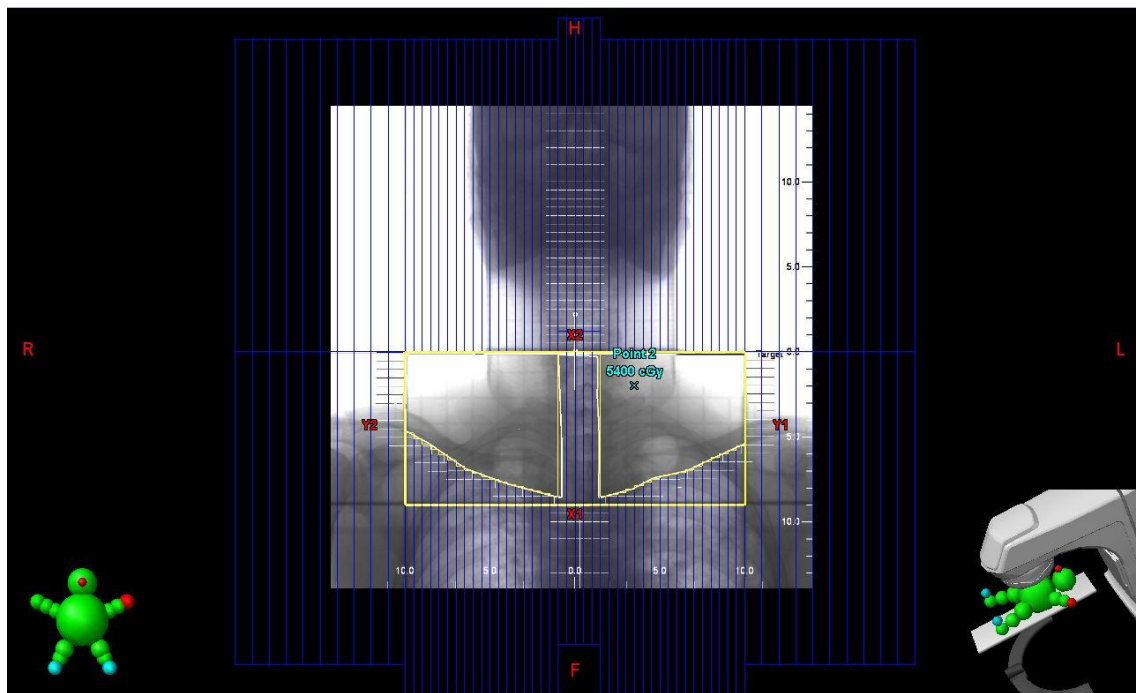


Figure shows 2D planning with MLC shielding of anterior field

After completing 45Gy of external beam radiation in two opposing lateral fields the posterior border is shifted anterior to spinal cord to spare the spinal cord.

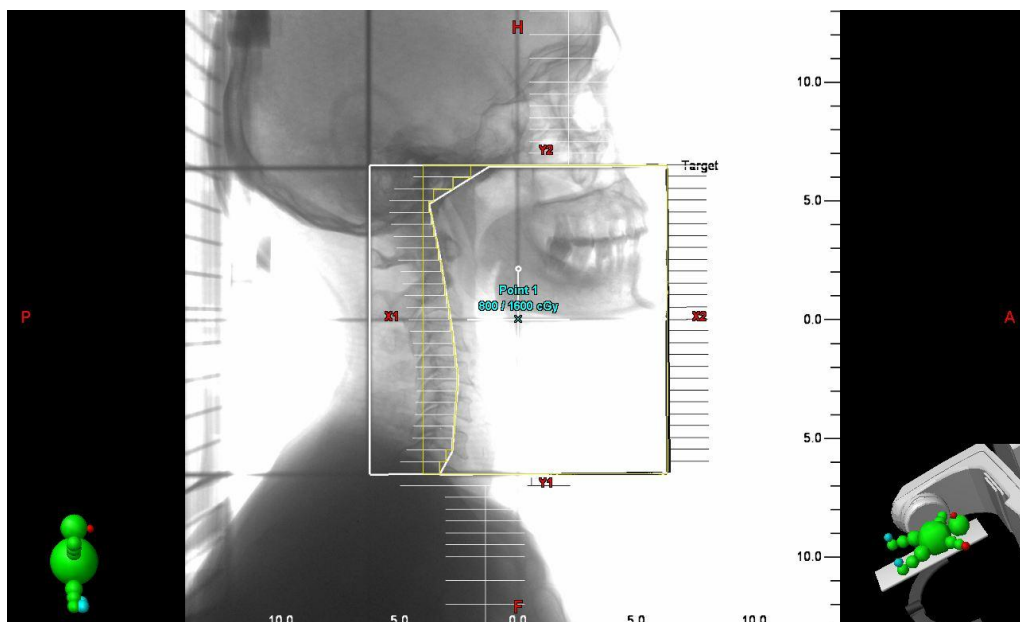


Figure shows 2D off cord planning with MLC shielding of lateral field

### **3D CONFORMAL TECHNIQUE:**

In conformal technique target volume is defined with three dimensions view for contouring purpose. It has multiple beams because to reduce the normal tissue toxicity and confined dose to the target alone. But concavity not archived in conformal technique. Setup errors also present in conformal technique. Contouring is drawing in CT scan in slice by slice and exact conformity we can achieve. Beam shaping done with multi-leaf collimators (MLC). It usually has 4 – 6 beam angles. It is 3D inemntional images will give precise treatment planning. In this no need to change the blocks during the treatment. Intensity of the beam is uniform.

#### **Planning CT scan:**

CT scan should be done from base of skull to arch of aorta with supine position of the patient with immobilization thermoplastic mould. In the CT scan will send to planning system, there is got registered in planning system, than we have do contouring the structure of the patients. This CT scan will be in axial

Cuts depending upon the technique we can take the slices from 0.25 cm, 0.5 cm and 0.75 cm.



### ICRU Volumes for contouring:

#### Gross Tumour Volume (GTV):

It is grossly demonstrable tumour, macroscopic lesion. Tumour is visible, palpable and demonstrable in imaging.

#### Clinical Target Volume (CTV):

It is demonstrable tumour and any other surrounding tissues with presumed tumour. It delineates

#### Planning Target Volume (PTV):

In this volume that includes CTV, setup margin and setup uncertainties.

#### Organ at risk (OAR):

Spinal cord, brain stem, brain, contralateral parotid, larynx and inferior constrictor. Tolerance doses are given in Table 4

OAR	Tolerance dose
Spinal cord	Max - 45Gy
Brain stem	Max – 54Gy
Brain	60Gy point dose
Contralateral parotid	Mean dose 26Gy
Larynx	Mean dose 40Gy
Inferior constrictor	Max 50Gy

### **IMRT (INTENSITY-MODULATED RADIATION THERAPY):**

Non uniform fluence of dose distributed to the patient with any given position of treatment beam to optimize the composite dose distribution. It also called as Inverse planning technique. It is to treat a patient with multiple number of beam direction non uniform fluence, it optimize high dose to target volume and low dose to surrounding normal tissue. In which we can achieve good dose conformity and steep dose gradient outside the target. It has two MLC window technique 1) dynamic MLC delivery, 2) step and shoot delivery.

Considerable factors in IMRT is increased cost, increased worked, increased treatment time/delivery, high integral dose, increased risk of second primary and low dose hypersensitivity. In head and neck cancers IMRT will spear major salivary glands and reduce xerostomia. Geographic miss due to improper positioning of the patient, organ motion and inadequate target delineation.

#### **Limitation of IMRT:**

Most dose distribution not physically achieved, distortion of internal anatomy, intrafraction motion and interfraction variation.

## **ALTERED FRACTIONATION SCHEDULES:**

During conventional fractionation using conformal and IMRT techniques are reduce normal tissue toxicities. But improving loco-regional control will achieve by increasing dose to tumour should be needed. In prolonged treatment time the tumour cell allow for repopulation. For that few newer fractionation schedule were tried. It is alerted fractionation.

### **Hyper-fractionation:**

It is increase daily fraction with reduce the daily dose, which will leads to decrease the overall treatment time. It will reduce late toxicities, increase tumour control and slightly increase acute toxicities.

### **Accelerated fractionation:**

It is increase daily fractions without alter the daily dose and decrease the overall treatment time. It will increase the local control, slight increase acute and late toxicities.

### **Hypo-fractionation:**

It is decrease total fractionation along with increase the daily dose. It decrease overall treatment time and increase local control. Acute toxicities are same with increase late toxicities.

**Accelerated repopulation:**

The cells are treated with cytotoxic agents (e.g Radiation) can trigger the surviving cells to divide faster than before. Analysis suggested that accelerated repopulation starts in human cancer cells about 4 weeks after starting radiation. So dose increment about 60 cGy/fraction will compensate the accelerated repopulation.

Pre-treatment doubling time for head and neck cancers is 30 to 60 days, but after radiation starts the doubling time is reduced to 3 - 5 days. In head and neck cancers each day delay during treatment will reduce the local control about from 0.4 to 2.5%. It is better to delay initiation of treatment than introduce delay during treatment. (18)

**CONCOMITANT BOOST:**

It is during the conventional fractionation boost dose is given in last two weeks radiation. It will counteract the accelerated repopulation. In boost treatment duration daily dose will decrease and gap between two fractions is 6 hour. It is increase loco-regional control and disease free survival. It will leads to more severe acute toxicities and no effect on late toxicities.

	Conventional fractionation	Hyper fractionation	Accelerated fractionation	Concomitant Boost
Total no of fractionation	30 fractionation	Increased	Same as conventional	Increased
Dose/ #	200cGy/ #	Decreased	Same as conventional	Decreased
Overall time	6 weeks	same/increased	Same as conventional	Decreased
No of #/day	1	> 1 fractionation	Increased	> 1 # in last 2weeks
Total dose	60Gy	Increased	Decreased	Decreased

## **SIMULTANEOUS INTEGRATED BOOST-INTENSITY MODULATED**

### **RADIOTHERAPY (SIB-IMRT)**

It is intuitive radiation technique. It will deliver extra boost simultaneously along with normal fractionation. It will increase to dose to target sub-volumes and reduce dose to critical structures. IMRT is using computer-optimized intensity distribution are controlled by dynamic MLCs will delivered multiple beam along with simultaneously irradiating nearby tissue in different dose in single treatment session. This technique will allows for improved dose conformity, excellent dose homogeneity within the target volumes, and conformal avoidance of adjacent critical normal tissues throughout the treatment course. Using this approach, the fractional dose delivered to gross tumour will be increased, at the same time the radiation doses and dose schedules are adequate for tumour control in marginal tissues and clinically

uninvolved lymph nodes are preserved. This approach is called as Simultaneous Integrated Boost (SIB). (19, 20, 21, 22, 23, 24, 25, 26)

### **Acute toxicities:**

#### **Mucositis:**

It is most common side effects of radiation and chemotherapy, But short term side effect. It depends on type ionizing radiation, dose of RT, rate of RT delivered. It cause pain which needs stop therapy to mucositis to heal. It is due to mitotic death of cells.

#### **RTOG grading of Mucositis:**

- 1) Grade I- Injection or mild pain.
- 2) Grade II- Patchy mucositis and moderate pain.
- 3) Grade III- Confluent fibrous mucositis and severe pain.
- 4) Grade IV- Ulceration, haemorrhage and necrosis.

#### **RTOG grading of Dermatitis:**

- 1) Grade I- Faint or dull erythema, epilation,
- 2) Grade II- Bright erythema, patchy moist desquamation,
- 3) Grade III- Confluent moist desquamation other than skinfolds,
- 4) Grade IV- Ulceration, haemorrhage and necrosis.

**RTOG grading of Dysphagia:**

- 1) Grade I- Mild dysphagia may require soft diet,
- 2) Grade II- Moderate dysphagia may require liquid diet,
- 3) Grade III- Severe dysphagia may require IV fluids, NG tube insertion.
- 4) Grade IV- complete obstruction, ulceration, perforation and fistula.

**Late toxicities:**

- 1) Xerostomia
- 2) Dysphagia
- 3) Taste alterations
- 4) Osteoradionecrosis

## **CHEMOTHERAPY:**

### Cisplatin (cis-diamminedichloroplatinum) (CDDP)

It is used in wide variety of cancers, it is a prototype drug and alkylating agent. It has high affinity to electrons so it increase sensitive of radiation.

#### Mechanism of action:

- 1) Inhibition of DNA synthesis,
- 2) Inhibition of transcription elongation by DNA cross links,
- 3) Inhibition of repair of radiation induced DNA damage.

#### Dose regimen:

- 1) 100 mg/m<sup>2</sup> or 70 mg/m<sup>2</sup> IV every 3 weekly for 3 cycles,
- 2) 40 mg/m<sup>2</sup> IV every weekly for 6 cycles.

#### Administration:

- 1) Monitoring with serum creatinine, electrolyte, magnesium and calcium.
- 2) Antiemetics: we should started with ondansetron, dexamethasone.
- 3) Hydration: we have hydrate the patient with adequate Intravenous fluids and administration of KCL and MgSO<sub>4</sub> infusions during delivery.



### Toxicity:

Dose limiting toxicity are acute renal failure, peripheral neuropathy (cumulative dose  $>400\text{mg/m}^2$ ) and ototoxicity (Dose  $> 100\text{ mg/m}^2$ ). Common side effects are severe nausea, vomiting will happened all patients, it will leads to electrolyte imbalance. Other common side effects are anorexia, metallic taste of foods, myelosuppression and sterility. Other occasional side effects are SIADH, cortical blindness, congestive cardiac failure and tetany.

### Indication:

- 1) Unresectable squamous cell head and neck cancers,
- 2) Nasopharyngeal cancer,
- 3) Laryngeal cancer,
- 4) Postoperative

## **II.AIM:**

To evaluate the feasibility of hybrid simultaneous integrated boost (SIB) technique and its efficacy in the treatment of locally advanced carcinoma tongue.

**Inclusion Criteria:**

- 1) ECOG performance score: 0-2,
- 2) Age 30-60 years,
- 3) Both sexes
- 4) Locally advanced carcinoma anterior 2/3<sup>rd</sup> tongue  
(T4a, N1, 2 & 3, M0),
- 5) Patient is planned for definitive concurrent chemo radiation  
(3 weekly Cisplatin 70 mg/m<sup>2</sup>)
- 6) Histopathology: Squamous cell carcinoma.
- 7) Non metastatic disease.
- 8) Adequate blood function test,
- 9) Written informed consent for the study.

**Exclusion Criteria:**

- 1) Patients with poor performance status (3 & 4),
- 2) Patients initially treated with Radiation therapy, Chemotherapy and surgery,
- 3) Patients who had other histology: adenocarcinoma, melanoma and lymphoma.
- 4) Patients with palliative intent of treatment,
- 5) Patients who has not willing to participate in this study,
- 6) Patients with previously diagnosed as parotid glands disorder ( e.g Sjogren's syndrome)
- 7) Patients with predisposing to enhancing radio sensitivity (e.g ataxiatelangiectasia or past/active connective tissue disorders).
- 8) Uncontrolled comorbidity

### **III.MATERIAL AND METHODS:**

All patients who came to Cancer Institute were examined thoroughly. Most of the patients were referred by non-oncology physicians. Diagnostic and staging investigations are done on outpatient basis. After conforming non-metastatic squamous cell carcinoma of oral tongue. Patient with stage IVa and IVb were enrolled in the study. Patients were counselled clearly about treatment modality, technique, toxicities and disease outcome. After getting informed consent these patients were enrolled into our study.

All patients were advised about the importance of proper nutritional, encouraged to avoid spicy food. All patients were Counselling for strict cessation of smoking and/or tobacco chewing habits, Clearly explained that smoking or tobacco chewing during treatment will reduce the treatment outcome and will also increase the risk of occurrence of second primary in aero-digestive track. . They were explained about the importance of oral hygiene All patients underwent dental examination and if needed dental extraction done. Patients were all admitted in ward.

Thermoplastic mould was done to immobilise patients in supine position, with custom made mouth bite to depress the tongue.

Planning CT scan done for all patients in flat couch from base of skull to arch of aorta with thermoplastic mould.

### **Treatment:**

All patients were planned for concurrent chemo-radiation. Chemotherapy schedule was 70 mg/m<sup>2</sup> Cisplatin in day 1, 22 and 43.

Radiation was designed to be delivered in two phases. All patients were treated with 6 MV photons in 600c unit at our institute.

Treatment was delivered in two phases as planned.

#### **Phase I:**

Patient were treated with 6 MV X-ray beam therapy to deliver a Total Dose of 36Gy using conformal technique with 200cGy daily dose per fraction for 5 days/week over 3.5 week

In this phase PTV includes primary tumour and bilateral whole neck nodes along with setup error margins. This area received TD 36Gy in phase I. After completion 36Gy all patients were underwent re-planning. A repeat Mould and repeat CT scan.

#### **Phase II:**

It has two PTV's, the high risk PTV (residual primary and residual neck nodes) and the low risk PTV (the entire PTV contoured in phase I excluding the

cord) were contoured. Patients were treated with 6 MV X-ray beam therapy using IMRT technique.

A Total Dose of 24Gy as 240cGy/day to the high risk PTV and a Total Dose of 20Gy as 200cGy/day to the low risk PTV was delivered simultaneously in 10 days over 2 weeks.

Chemotherapy delivered was three weekly Cisplatin.

These patients were compared with 10 matched control patients treated in 2015 with conformal technique TD 60Gy (200cGy/day), 5 days per week, over 6 - 7 weeks concurrent with chemotherapy.

During the treatment all patients are advised to take a proper nutritional support. They are advised to do sodium bicarbonate mouth wash 6-8 times per day, to avoid tooth brushing in order avoid mucosal injury. All patients were advised to have non-spicy soft bland easily digestible high protein diet with added salt. They were all advised to take more vegetables, more water intake to reduce renal toxicity by Cisplatin. They were also told to avoid hot or chilled food as it may aggravate mucositis. Multivitamins and antioxidants were given daily for all patient. Patients were started on chymmerol forte at around the end of third week of treatment. Amifostine is not usually administered at our institute. During the treatment time good psychological support were given to all patient and moral support also given.

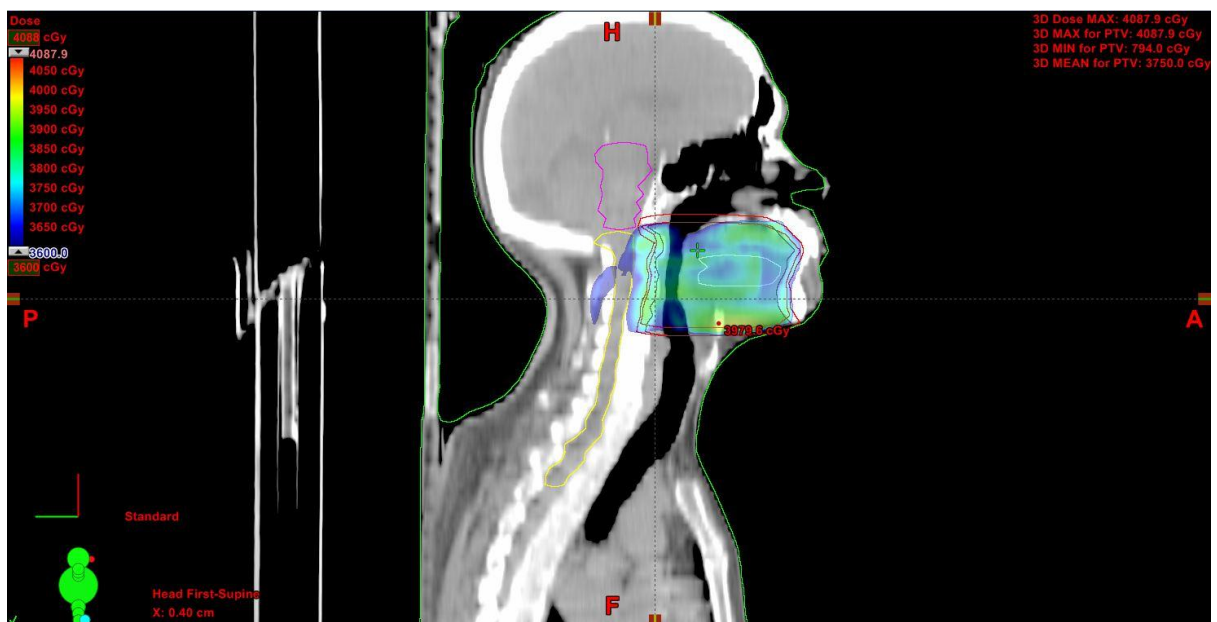
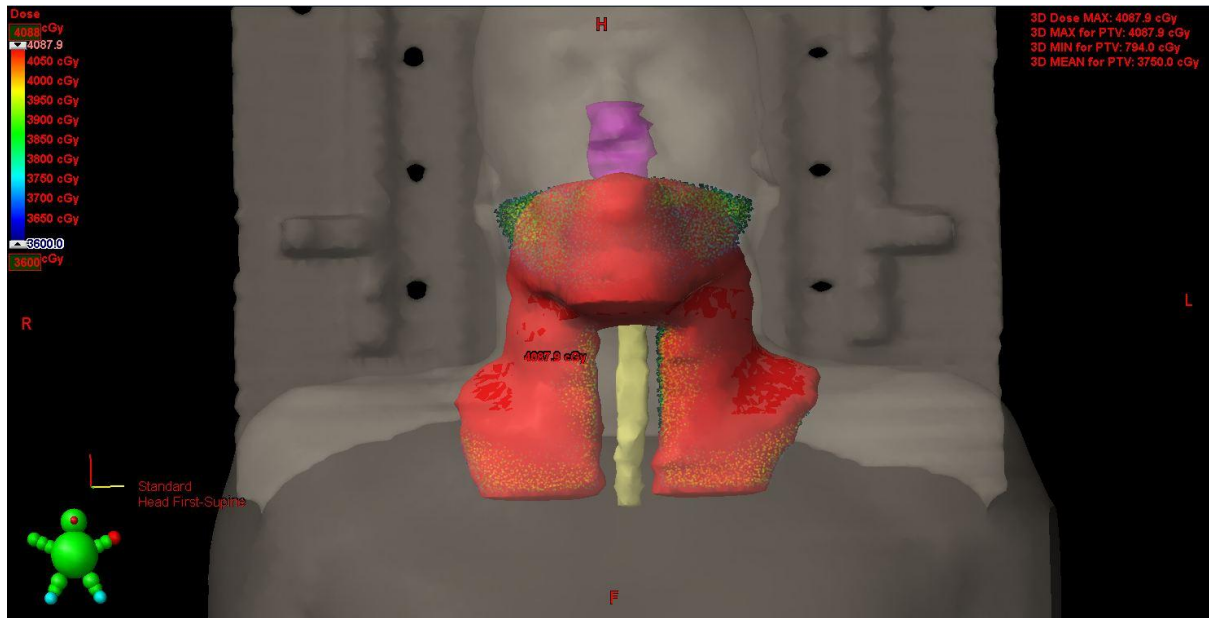




Figure shows dose distribution of 3DCRT plan (Sagittal plane)

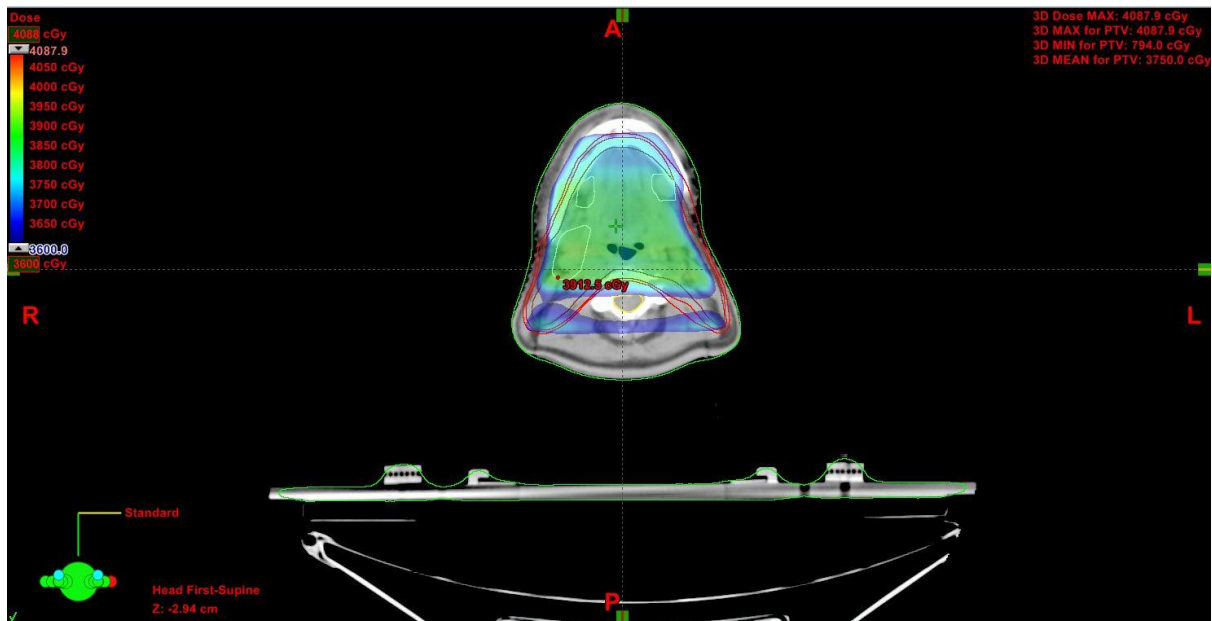


Figure shows dose distribution of 3DCRT plan (Transverse plane)

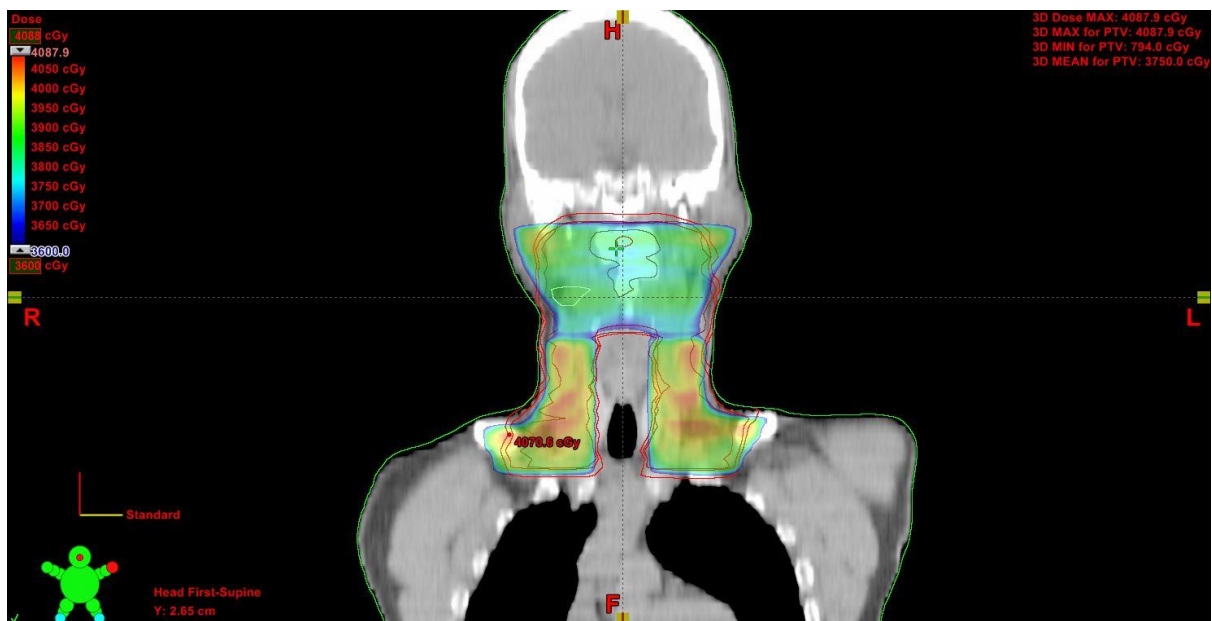


Figure shows dose distribution of 3DCRT plan (Coronal plane)

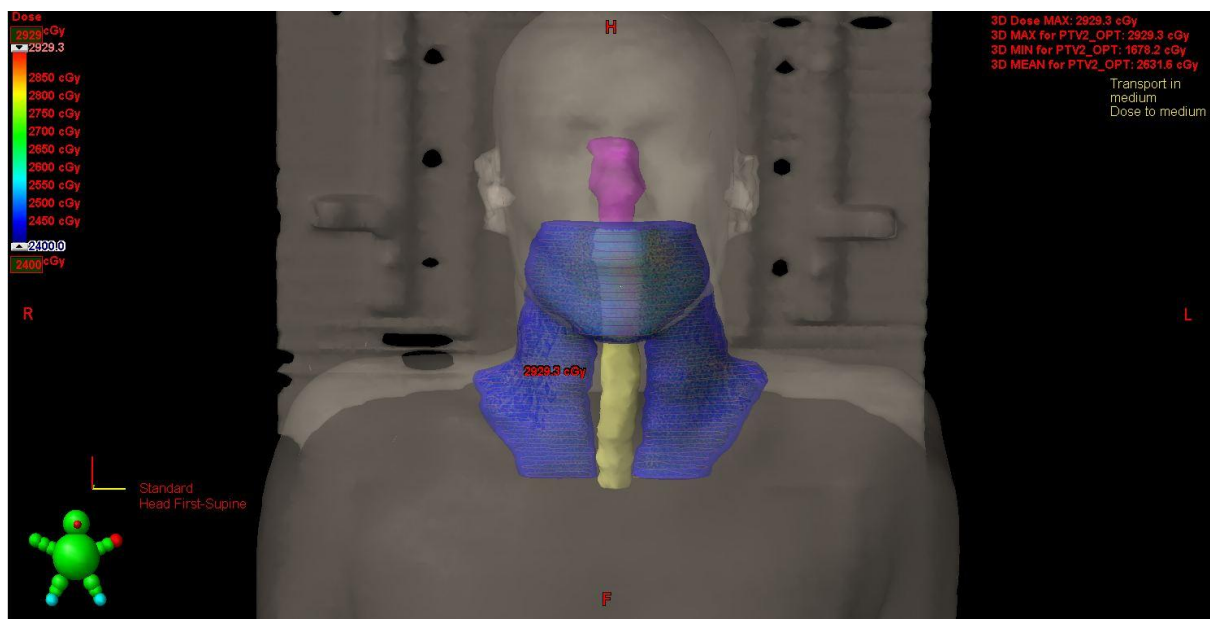


Figure shows 3D representation of PTV in SIB-IMRT plan

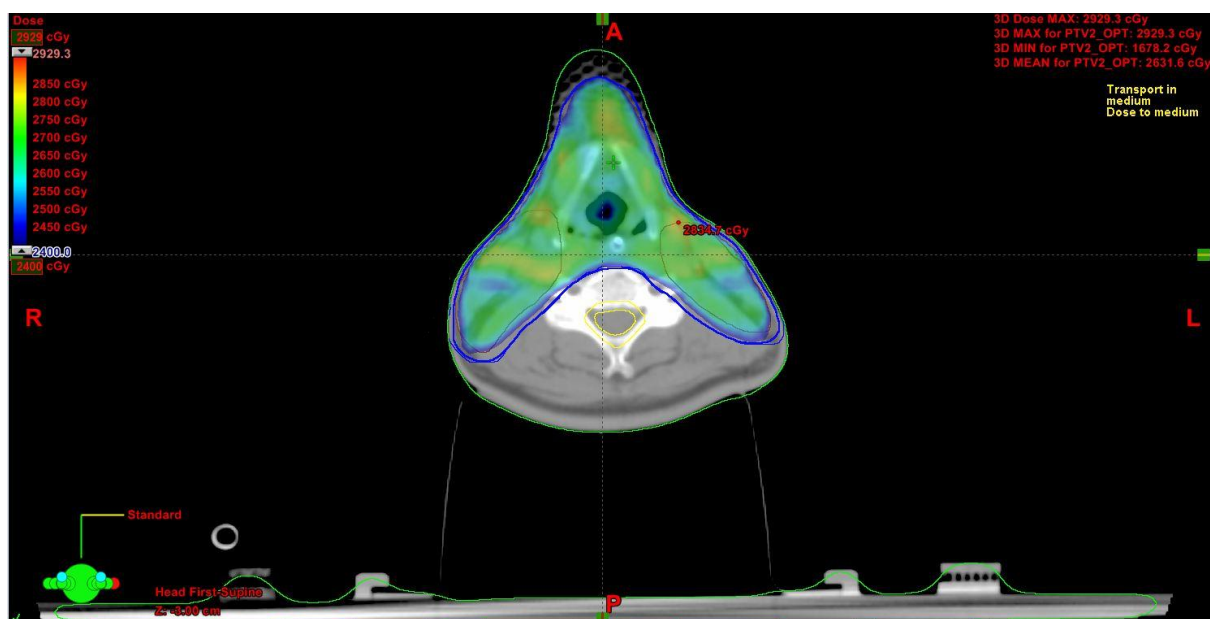


Figure shows dose distribution of SIB-IMRT plan (Transverse plane)

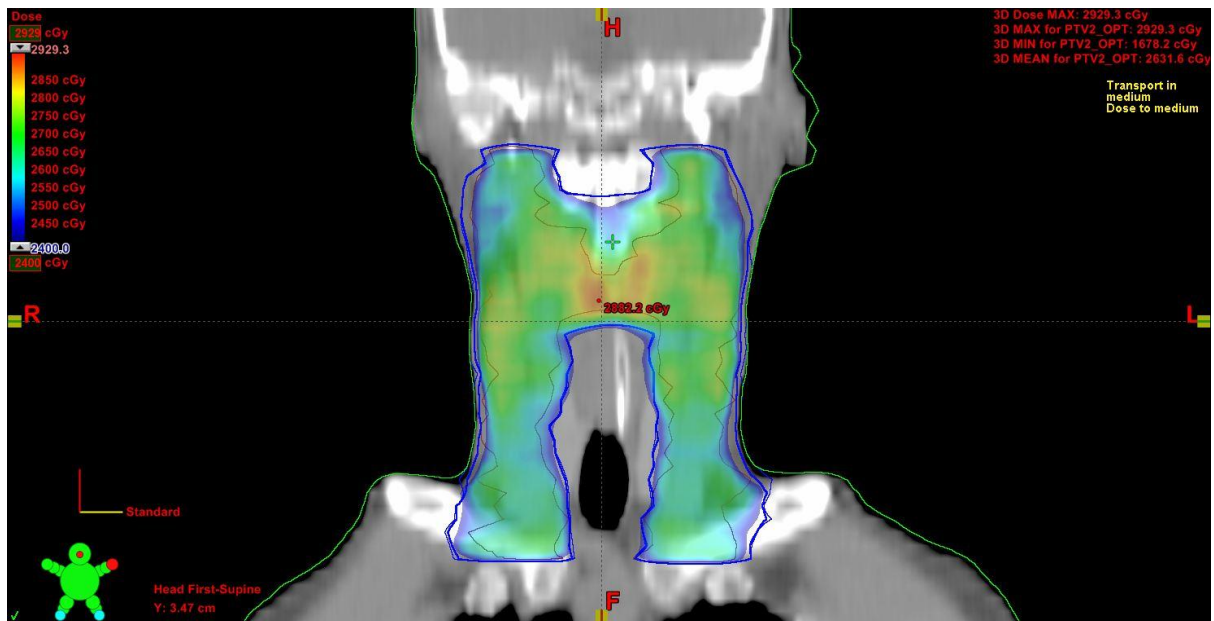


Figure shows dose distribution of SIB-IMRT plan (Coronal plane)

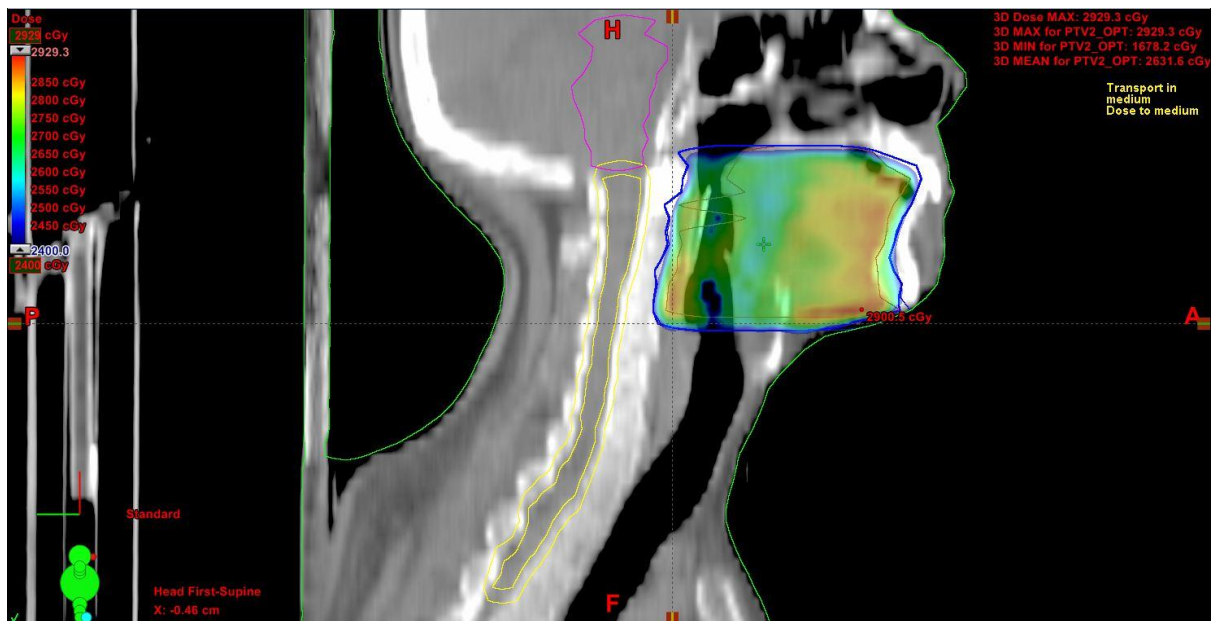


Figure shows dose distribution of SIB-IMRT plan (Sagittal plane)

### **Toxicity Assessment and management:**

All patients were assessed for tumour response for primary, nodal region and acute toxicity during the treatment period on weekly basis.

During the radiation treatment patients developed acute toxicity like mucositis, dermatitis and dysphagia. These patients advised for conservative management. Patients with mucositis were advised for frequent mouth wash, lignocaine viscous gel/Mucaine gel for pain relief. Opioids and NSAIDS in the form of tramadol or ibuprofen along with paracetamol were used for relief of mucositis/dermatitis induced pain when ever needed. Patients who developed grade III acute toxicities advised for Naso-gastric tube insertion for better nutritional support.

Before delivering chemotherapy all patient's complete blood count, renal function test, liver function test and serum electrolytes was checked. Chemotherapy was delivered only if all blood investigation were normal, patient vitals are stable and hydration was adequate. If investigation are de-arranged patient was admitted to ward and conservative management was given to that patients along with pending that schedule of chemotherapy or radiation.

During treatment weekly twice white blood cell count was checked for all patients.

**Response assessment:**

Patient response to treatment is assessed 6 weeks after completion of treatment according to World health organization criteria for solid tumour.

Local disease control is evaluated by clinical examination and imaging and biopsy is done whenever necessary. For each follow up review complete physical examination, response assessment and toxicities assessment were done.

**Response Evaluation Criteria in Solid Tumours (RECIST)**

1. Complete response (CR): disappearance of all known disease by two observations not less than four weeks apart.
2. Partial response (PR): 50 % or more decrease the tumour size by two observations not less than four weeks apart.
3. No changes (NC): 50 % decrease in tumour size not assessed and more than 25% decrease in tumour size assessed.
4. Progressive disease (PD): 25 % more increase the tumour size or new lesion appearance.

#### **IV.RESULTS:**

From September 2015 to august 2016, there were total    number of case diagnosed with carcinoma tongue, were stage IV, Twelve patients fit in to the inclusion criteria. These twelve patients with locally advanced carcinoma tongue stage IVA and IVB were enrolled in to study after taking a written informed consent. But, one patient had tumour bleeding at 6Gy itself so patient was treated with haemostatic radiation to tongue TD 500cGy in two fractionation. Hence, patient in not included in this study. Another one patient had progressive disease in the form of nodal region ulcerated and development of post auricular nodes was treated with palliative radiation. Hence this patient also not included in this study. Total ten patients were assessed in the study. All the 10 patient completed the treatment.

#### **Patient characteristics:**

Median age of 43.7years (range of 39 to 65 years), all are male patients diagnosed to have stage IVa carcinoma tongue. In this patients 4 patients were smoker and 5 were chewing, one patient having both the habits of smoking and chewing. Size of primary lesion ranging from 5 x 3

cm to 8 x 7 cm. Seven patients had tumour in the ventral surface of the tongue, two patients had extensive tumour occupying entire tongue, one patients alone tumour was limited to lateral border. Clinically two patients had no neck nodes palpable, two patients had ipsi lateral single node < 3 cm, one patient had ipsi lateral node 4cm, four patients had multiple ipsi lateral nodes < 6 cm, and one patients had bilateral neck nodes < 6 cm.

**Acute toxicity:**

During course of treatment at 30Gy two patients developed Grade I mucositis and four patients had grade II mucositis who progresses to have Grade III mucositis at the end of first phase of treatment requiring treatment break.

At the end of first phase four patients had grade I mucositis, two patients had grade II mucositis and four patients had grade III mucositis. At the end of treatment two patients each developed Grade I, II and III mucositis. None had grade IV mucositis. Two patients developed oral candidiasis were treated with local anti-fungal.

Five patients had Grade II-III dysphagia requiring nutrition support in the form of Ryles tube and Intravenous fluids.

Six patients had dry desquamation of skin field area, two patients had moderate dermatitis at the end of treatment.

At some points of treatment only two patients developed grade III neutropenia with nadir ANC-900/Cu mm. These patients are managed with prophylactic IV antibiotics. None of the patient developed febrile neutropenia. These two patients received Inj. GCSF (Granulocyte colony stimulating factor) for 5 days. During this time patient was treated with radiation.

#### **Treatment break:**

Out of ten patients three patients had a treatment break of more than 10 days owing to Grade III mucositis, 2 patients also had Grade III neutropenia. All patient put together had a mean treatment break 7.2 days ranging from 3 to 12 days.

#### **Completion of chemotherapy:**

Out of the ten patients five patients all the three cycles of chemotherapy on scheduled time. Four patients had only two cycles chemotherapy, one patient had only one cycle of chemotherapy. None of the patient had other Cisplatin complications like ototoxicity, nephrotoxicity and peripheral neuropathy other complication.

#### **Treatment results:**

Out of ten patients four patient had a satisfactory primary tumour regression, eight patient had complete nodal regression. At 3 months after



the end of treatment all four patients continue to have good loco-regional control, one patient had static response and remaining five patients had residual disease.

### **Follow up:**

All patients were reviewed after 6 weeks for assessing the first follow up. Then all patients were regular assessed by monthly once for one year. After that patients will be follow up by three months once for two years, than six months once for two more years after that annual follow up.

### **Retrospective Control group:**

Retrospective data of patients diagnosed as carcinoma tongue and treated with concurrent chemo-radiation using conformal technique in conventional fractionation in our institute in the year 2015 was collected. Of these, ten patients matched for age, stage, site of tumour were taken as control group and analysed in detail and compared with the study group.

### **Comparison:**

In age distribution analysis younger age (< 40 years) patients are well response to treatment compared to old age (> 50 years) patients in both study group and control group. Loco-regional control are more in young

age patients. Elderly age patients are not tolerate the chemotherapy and more acute toxicities and treatment breaks are more in both groups.

Loco-regional response with respect to different age group:

AGE Years	Study group (10)	LR response	Control group (10)	LR response
< 40	4	2	3	2
40-50	4	2	4	1
50-60	1	0	2	0
>60	1	0	1	0

In study group all patients are having smoking /or tobacco chewing habits. Tobacco chewing having more incidence of oral cavity cancer compared smoking habit. Compare to both group smoker are less response to treatment compared with tobacco chewer.

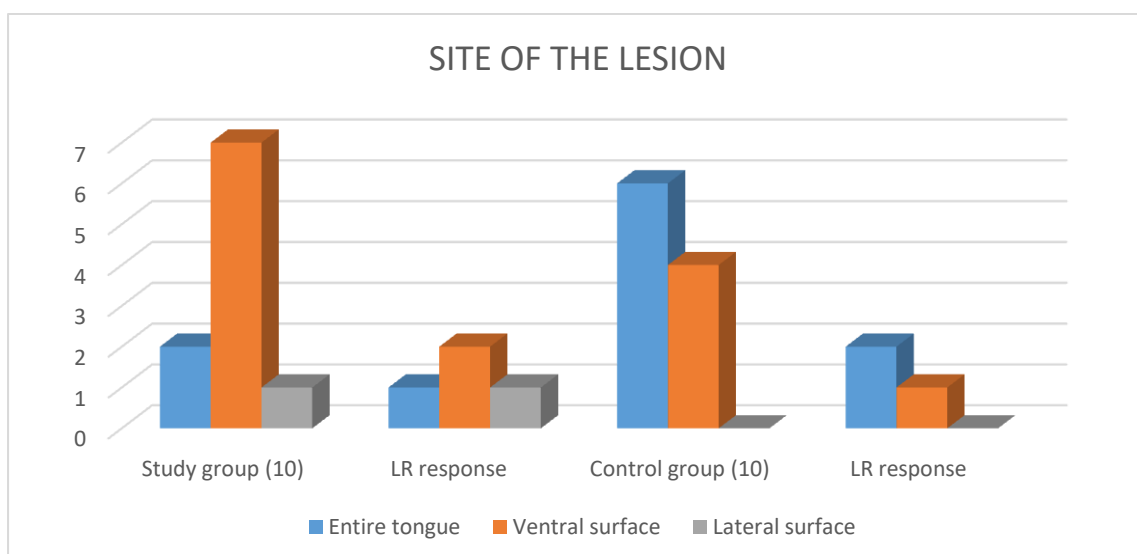
Loco-regional control with respect to habits:

HABITS	Study group (10)	LR response	Control group (10)	LR response
Smoking	4	1	2	0

Chewing	5	3	5	2
No habits	0	0	1	1
Both habits	1	0	2	0

In study group seven patients are ventral surface of tongue, two patients are entire tongue and one patient is lateral surface involvement. In control group six patients are entire tongue and four patients are ventral surface involvement present. Both entire tongue and ventral surface tongue are poor prognosis patients. Compared in both ventral surface tongue patients response to treatment is well on both group. Ventral surface tongue we cannot assess the deeper invasion of the tumour. Hence it is consider bad prognosis.

Loco-regional control with respect to site of the lesion

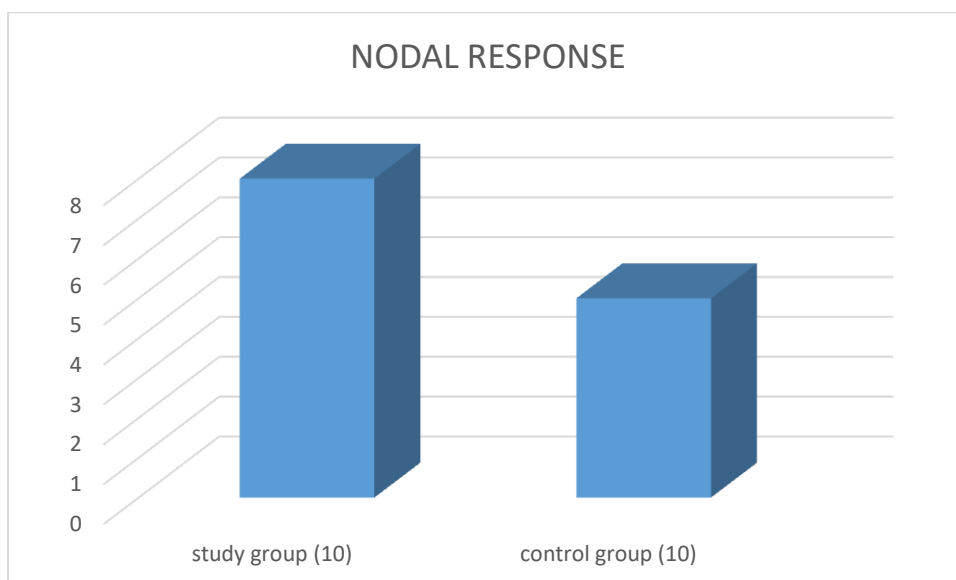


In our study nodal stage more than N2b not response well compared to nodal stage N1 and N2a. The study group having two patients are N1 node and one patient is N2a node were responded well to the treatment. Among the four patient were having N2b nodes three patient responded well. In control group two patients having N1 node and two patients were having N2c were responded well. Along five patients having N2b node two patients only responded only.

NODE	Study group (10)	Node regression	Control group (10)	Node regression
N0	2	2	0	0
N1	2	2	2	2
N2a	1	1	0	0
N2b	4	3	5	2
N2c	1	0	2	1
N3	0	0	1	0

In nodal response is 80% vs 50% ( $p=0.16$ ) in study group and control group respectively

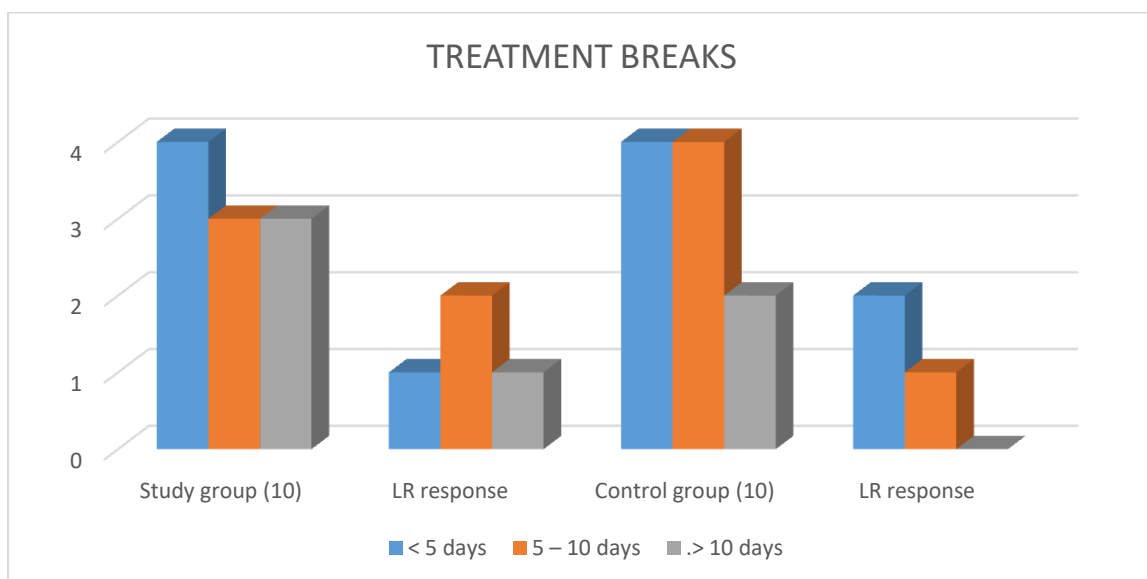
NODE	Study group (10)	LR response	Control group (10)	LR response
N0	2	0	0	0
N1	2	2	2	0
N2a	1	1	0	0
N2b	4	1	5	2
N2c	1	0	2	1
N3	0	0	1	0



### Treatment breaks:

Treatment breaks are comparable in both groups. There are four patient having < 5 days treatment in both group for which response is one and two patients respectively. In 5 – 10 days treatment break were three in study group and four in control group, among them response well were two patients in study group and one patient in control group. In more than 10 days treatment break three patients in study group and two patients in control group, among them in study group one patient responded well compared to control group none of the responded.

Loco-regional control with respect to treatment break:



In comparing tumour size, small size tumours were responded well in both group. In contrast study group on patient had tumour size of 8 x 7 cm tumour responded well with hybrid technique. In study group 5 cm tumours responded well comparable with control group. Five patients were having the tumour size of 6 x 5 cm in study group none the patients responded. Four patients were having tumour size of 6 x 4 cm in control group none of them responded. In study group four patients responded well compared to control group three were responded well. Large volume tumour response usually poor in both group.

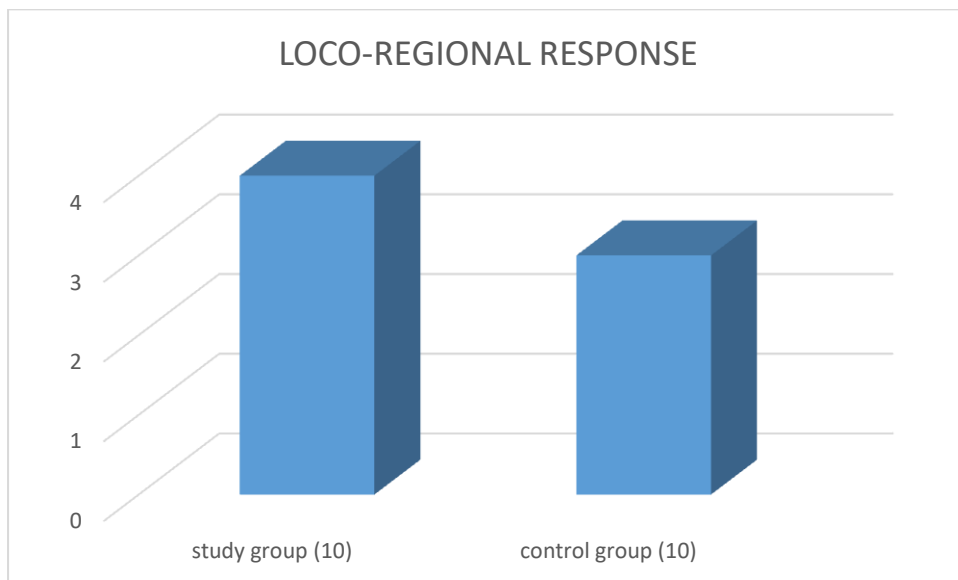
Loco-regional control with respect to volume of tumour

SIZE	Study group (10)	LR response	Control group (10)	LR response
5 x 3 cm	2	2	2	1
5 x 5 cm	0	0	2	2
6 x 4 cm	1	1	4	0
6 x 5 cm	5	0	1	0
7 x 6 cm	1	0	1	0
8 x 7 cm	1	1	0	0

### **Loco-regional response:**

In study group among the ten patients four responded well with hybrid simultaneous integrated boost technique. In control group among the ten patients three patients responded well. The p value is 0.639.

The loco-regional response is slightly better in study group compared to control group. But, the p value is not significant in this study because of poor response of the disease.



### **Statistical Analysis:**

The loco-regional response and toxicity profile was analysed by Kaplan-Meier method. P value was also calculated in chi-square test.



## **V.DISCUSSION:**

Management of tongue cancer depends on extent of primary tumour and nodal status. The options are radical RT with or without neck dissection and primary surgery with or without postoperative RT. Definitive/ Initial Radiotherapy has a benefit mainly due to functional preservation. Base of tongue tumours are more radiosensitive than oral tongue. Overall treatment time plays a major role in local control.

For locally advanced head and neck cancer treated with primary radiation, It is believed that radiation alone is inferior therefore the current standard of care is concurrent chemo-radiation. Concurrent chemotherapy along with altered fractionation is superior in the form of loco-regional control and comparable toxicity profile.

External Beam Radiotherapy up to 40Gy followed interstitial brachytherapy. Decroix and Ghissein study showed combine external beam radiation and brachytherapy to be beneficial.

Brachytherapy gives the benefit of function preservation, which is achieved through tissue preservation. Local control rates are 85% which are on par with that achieved by surgery. Local control rates decrease with increasing tumour size.

Using Linear-quadratic modal we can compare the radiation dose of two different technique by using Biologic Effectiveness Dose (BED).

$$\text{BED} = (\text{total dose}) \times (\text{relative effectiveness})$$

$$\text{BED} = (nd) \times (1 + d / \alpha/\beta)$$

For 200cGy conventional fractionation schedule for TD 60Gy

$$\text{BED} = 30 \times 2 (1 + 2/10) = 72\text{Gy}$$

In study group patient was treated with two phase of treatment.

In phase I, they were treated with 200cGy per fractionation for TD of 36Gy over 18 fractions. The BED of this schedule is

$$\text{BED } 36 = 18 \times 2 (1 + 2/10) = 43.2\text{Gy}$$

In phase II, they were treated with 240cGy per fractionation for TD of 24Gy over 10 fractions. The BED of this schedule is

$$\text{BED } 24 = 10 \times 2.4 (1 + 2.4/10) = 29.76\text{Gy}.$$

Total BED of the study group is  $43.2 + 29.76 = 73\text{Gy}$ .

In study group BED compare to control group BED is more in 1Gy.

## **HYBRID TECHNIQUE:**

Locally advanced squamous cell carcinoma of tongue cause major burden of disease. It needs aggressive treatment for satisfactory loco-regional control.

Radical surgery is not feasible and more surgical morbidity. Therefore chemoradiation is the main modality of treatment in locally advanced tongue cancer.

In standard fractionation schedule will achieve limited loco-regional control. Therefore the newer approach to evaluate the altered fractionation for better loco-regional control and overall survival. In altered fractionation concomitant boost technique causes better loco-regional control achieved compared with other techniques. In this study we were attempted hybrid simultaneous integrated boost technique for treating locally advanced carcinoma tongue.

RTOG 90-03 study:

Improvement on disease free survival is 8 % in hyper-fractionation, accelerated concomitant boost fractionation compared to standard fractionation. (27) In this hyper-fractionation having high cost, more work compared to concomitant boost technique. There will be an inconvenience for multiple fractionation will leads to more acute toxicity. It will increase the workload of radiation treatment units, technologist, physicist and radiation oncologist. In our study we can escalate the dose in phase II will be like concomitant boost technique.

### **Accelerated repopulation:**

During end of treatment accelerated repopulation of tumour cell are more it will leads to tumour proliferation. In this study designed for additional dose given during end of treatment will compensate the accelerated repopulation.

Concomitant boost radiation is reduce the treatment duration. It leads to counteract the accelerated repopulation of clonogenic cells on radiation.(28)

In contrast to concomitant boost technique in this study patients were treated with single fractionation schedule not in concomitant boost technique patient was treated two fraction for 2 weeks with 6 hours gap. This will reduce the workload of machine and manpower especially in large volume patient treating radiation centres (29). In this centres we cannot treat all patients with advance radiation technique. Because this will consume more treatment time of the machine and working staffs. For that we attempted hybrid simultaneous integrated boost technique for locally advanced tongue cancers (30).

Ghoshal et al studied 216 patients with oropharyngeal cancers treated with concomitant boost radiation and compared with concurrent chemo-radiation. Median treatment break was 11 days but in our study 7.3 days. Hospital admission needed was 54% but my study 20%. Grade III Mucositis were 54% comparable with standard conventional fractionation. Loco-regional response is 74% Vs 68% ( $p=0.3$ ) and partial response were 25% and 22% reported (31).

2 years disease free survival in this study is 61% ( $p=0.2$ ).

Acute toxicities Grade III mucositis were 55% and 38%. Grade III dermatitis were 61% and 27%. Grade III dysphagia were 34% and 42%.

Bhavana rai et al 60 patients of locally advanced head and neck cancer were compared concomitant boost chemo-radiation vs standard concurrent chemo-radiation. Local control for both arm had no significant difference (54% vs 49%) but toxicity profile were comparable. In acute toxicities Grade III mucositis were 43.5% and 48.2%. Grade II or more dermatitis were 78.3% and 81.7%. Grade II or more dysphagia were 87.2% and 96.4%. Grade II or more weight loss were 57% and 75.2%. Compare to our study local control were 40% and 30%. Acute toxicities were Grade III mucositis were 60% and 40%. Grade III dermatitis were 40% and 40%. Grade III dysphagia were 20% and 30%. Ryles tube insertion were 50% and 50% (32).

Sabine Bieri et al 42 locally advanced oro-pharyngeal cancer was treated with concomitant boost technique from May 1991 to October 1995. Local control after 3 years 79% and 61% ( $p=0.005$ ). Acute toxicities like Grade III mucositis were 78%, grade III dysphagia were 68 and 25%, ryles tube insertion were 68% and 14%.(33)

In the University of Texas M.D Anderson Cancer Centre, a study was done with increasing fractionation after 12 days of initial radiation. It is based on incremental dose needed to compensate the cancer cell proliferation at near the end of radiation treatment (34).

### **SIB:**

SIB-IMRT is more needed in busy radiation treatment centre with limited treatment machine and manpower. Because it is single daily treatment with escalating dose to target volume. This dose escalation radio biologically will toxicity to late responding normal tissue near or inside the GTV receiving higher dose. For that in this study dose escalation done towards end of therapy. Treatment breaks is due to acute toxicity. To overcome the repopulation during this treatment break. Increase dose per fraction and or number of fraction in a week can be increased.

Davide et al there were 50 patients head neck cancer enrolled in this study, they were treated with SIB 70 and SIB 66 schedules. In SIB 70 three target volumes were contoured (70Gy, 60Gy and 54Gy in 33 fractions), in SIB

66 three target volumes were contoured (66Gy, 60Gy and 54Gy in 33 fractions). At two years follow up local control were 91% and overall survival rate were 82.4%. Acute toxicities were Grade III mucositis 10%, Grade III dermatitis 6%, Grade III dysphagia 6% and Grade III xerostomia 4%. None of the patient had Grade IV toxicity. This study conclude that SIB-IMRT is safe and highly effective technique for treatment of head and neck cancers (35).

Chakraborty et al there were 28 patients head and neck cancer patients enrolled in this study were treated with SIB 72 and SIB 66 schedules. In SIB 72 target volumes were contoured (72Gy, 66Gy and 57Gy in 33 fraction) and in SIB 66(66Gy, 60Gy and 54Gy in 33 fraction). In follow up one out of 28 patients had local recurrence. None of the patients had distant metastasis. Acute toxicities were Grade III mucositis 42.9%, Grade III dermatitis 14.3% and Grade III xerostomia 10.7%. (36)

#### Concurrent chemo-radiation:

Pignon et al meta-analysis combined 93 randomized trials (37). It showed concurrent chemo-radiation will increase the overall survival in locally advanced head and neck cancer is about 5% and absolute benefit in survival 8% in five years (38,39, 40, 41).

Limitations of our study: We selected small number of patients, stage Iva tongue with ventral surface and entire tongue patients,

## **VI.CONCLUSION**

Hybrid simultaneous integrated boost (SIB) technique appears to be a feasible technique concurrent with chemotherapy in terms of better local control and comparable toxicity profile. Long term follow up to assess overall survival is needed before definitive conclusions can be made. Definitive conclusion can be obtained only if large volume of primitive early disease is analysed in future.



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